Bronchiectasis in India

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Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry

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Summary

Background Bronchiectasis is a common but neglected chronic lung disease. Most epidemiological data are limited to cohorts from Europe and the USA, with few data from low-income and middle-income countries. We therefore aimed to describe the characteristics, severity of disease, microbiology, and treatment of patients with bronchiectasis in India.

Methods The Indian bronchiectasis registry is a multicentre, prospective, observational cohort study. Adult patients (≥18 years) with CT-confirmed bronchiectasis were enrolled from 31 centres across India. Patients with bronchiectasis due to cystic fibrosis or traction bronchiectasis associated with another respiratory disorder were excluded. Data were collected at baseline (recruitment) with follow-up visits taking place once per year. Comprehensive clinical data were collected through the European Multicentre Bronchiectasis Audit and Research Collaboration registry platform. Underlying aetiology of bronchiectasis, as well as treatment and risk factors for bronchiectasis were analysed in the Indian bronchiectasis registry. Comparisons of demographics were made with published European and US registries, and quality of care was benchmarked against the 2017 European Respiratory Society guidelines.

Findings From June 1, 2015, to Sept 1, 2017, 2195 patients were enrolled. Marked differences were observed between India, Europe, and the USA. Patients in India were younger (median age 56 years [IQR 41–66] *vs* the European and US registries; p<0·0001]) and more likely to be men (1249 [56·9%] of 2195). Previous tuberculosis (780 [35·5%] of 2195) was the most frequent underlying cause of bronchiectasis and *Pseudomonas aeruginosa* was the most common organism in sputum culture (301 [13·7%]) in India. Risk factors for exacerbations included being of the male sex (adjusted incidence rate ratio 1·17, 95% CI 1·03–1·32; p=0·015), *P aeruginosa* infection (1·29, 1·10–1·50; p=0·001), a history of pulmonary tuberculosis (1·20, 1·07–1·34; p=0·002), modified Medical Research Council Dyspnoea score (1·32, 1·25–1·39; p<0·0001), daily sputum production (1·16, 1·03–1·30; p=0·013), and radiological severity of disease (1·03, 1·01–1·04; p<0·0001). Low adherence to guideline-recommended care was observed; only 388 patients were tested for allergic bronchopulmonary aspergillosis and 82 patients had been tested for immunoglobulins.

Interpretation Patients with bronchiectasis in India have more severe disease and have distinct characteristics from those reported in other countries. This study provides a benchmark to improve quality of care for patients with bronchiectasis in India.

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Introduction

Bronchiectasis is a growing global health problem. In Europe and the USA the reported prevalence of the disease has increased by more than 40% in the past 10 years.[1] Although substantial progress has occurred in understanding the epidemiology of bronchiectasis, large-scale

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Research in context

Evidence before this study

Bronchiectasis is a chronic respiratory disease causing cough, sputum production, and frequent chest infections leading to poor quality of life and high health-care resource utilisation. It is a frequent consequence of pulmonary tuberculosis infection, with a systematic review suggesting about 40% of survivors of tuberculosis infection develop radiological bronchiectasis. A recent published systematic review of MEDLINE from inception to 2018 for studies of the epidemiology and natural history of bronchiectasis identified that bronchiectasis is a common respiratory disease worldwide, affecting up to 566 per 100 000 population in high-income countries. Little published data are available from Asia, Africa, South America, or from low-income and middle-income countries more generally. The little data that are available suggest there might be considerable geographical variation in patient characteristics and management. However, no data for the burden of bronchiectasis in India exist. Disease registries can provide useful data for the epidemiology of disease.

Added value of this study

We developed a patient registry across 31 centres in India collecting comprehensive data for patient demographics, severity of disease, comorbidities, microbiology, and current treatment. Patients with bronchiectasis in India show marked differences to those previously reported in Europe and the USA. Patients in India were younger, more likely to be men, and showed a high frequency of severe, cystic bronchiectasis. Tuberculosis and other severe infections were the most frequently reported underlying cause. Indian patients had a high burden of symptoms and a high frequency of hospital admission for severe worsening of disease known as exacerbations. Patients were frequently and chronically infected with bacteria such as *Pseudomonas aeruginosa*. Markers of quality of care suggested that many patients in India do not currently receive evidence-based low-cost interventions such as chest physiotherapy. Previous tuberculosis infection was a risk factor for exacerbations.

Implications of all the available evidence

We identify risk factors for exacerbations and suggest areas for improvement in the care of bronchiectasis in India. Our study highlights the high severity and symptom burden associated with bronchiectasis in India and this is likely to be replicated in similar countries with a high prevalence of tuberculosis and severe respiratory infections. Bronchiectasis is a neglected disease and our data suggest a need for efforts to improve access to basic care interventions for bronchiectasis such as chest physiotherapy, vaccinations, and antibiotics. The discordance between patient characteristics in India compared with Europe and the USA suggest that data from high-income countries might not be generalisable to India and other Asian countries. There is a need to do interventional studies to demonstrate improvements in clinical outcomes specifically in Asian countries.

epidemiological data have been almost exclusively from European countries, the USA, and Australia.[2,3] Small cohorts from China and South America suggest that the characteristics of patients from low-income and middle-income countries might be different to those in Europe.[4,5] Patients with bronchiectasis in high-income countries are predominantly older and female, and approximately 40% are idiopathic.[2,3] The demographics, microbiology, severity of disease, and clinical phenotypes of bronchiectasis in low-income and middle-income countries such as India are not well described.

Understanding the heterogeneity of disease is currently the key research priority in bronchiectasis.[6,7] Several international randomised trials have not been able to meet their primary endpoints. It is speculated that this outcome is because different patients with bronchiectasis have different characteristics and treatment responses.[8–10] Most recently the RESPIRE programme[10] tested inhaled dry powder ciprofloxacin in patients with bronchiectasis and achieved positive results in RESPIRE-1,[8] which was done predominantly in Europe and the USA, but not in RESPIRE-2,[9] which was done predominantly in eastern Europe and Asia.[8–10] Multicentre randomised controlled trials have frequently taken place in low-income and middle-income countries where the characteristics of patients are not well understood. In Asia, tuberculosis is thought to be an important underlying cause of bronchiectasis.[11] Studies systematically doing CT in patients following treatment for tuberculosis have identified moderate or severe bronchiectasis in approximately 40% of patients, but data for the symptoms, lung function impairment, health-care resource utilisation, and treatment of these patients remain scarce.[12,13]

The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) was established in 2012 through the European Respiratory Society (ERS) to facilitate research in bronchiectasis across Europe.[14] In 2014, the EMBARC network partnered with the Respiratory Research Network of India to establish an Indian bronchiectasis registry. To our knowledge, this partnership is the first prospective multicentre bronchiectasis registry to be established in a lower-middle-income country. Herein, we report the first results of the Indian national bronchiectasis registry describing the clinical characteristics, severity of disease, and clinical phenotypes of bronchiectasis in India.

Methods

Study design and participants

The Indian bronchiectasis registry is a multicentre, prospective, observational cohort study. It is a non-interventional study, enrolling adult patients with

bronchiectasis across the country at 31 participating centres. Figure 1 shows the various participating sites across India. Patients fulfilling the inclusion criteria (aged ≥18 years with bronchiectasis on CT of the chest and the clinical syndrome of bronchiectasis defined by the presence of cough, sputum production, or recurrent respiratory infections) and not the exclusion criteria (inability to give informed consent, bronchiectasis due to cystic fibrosis, and traction bronchiectasis associated with interstitial lung disease or another respiratory disorder) were enrolled. The study was approved by the institution review boards of the participating centres. Patients gave written informed consent to participate in this study.

Assessments

Data were collected at baseline (recruitment) with follow-up visits taking place once per year. During the baseline and follow-up visits, comprehensive data were collected across various domains, including demographics, comorbidities, laboratory testing, lung function, exacerbations, disease impact, microbiology, radiology, and treatment and physiotherapy.

Lung function testing was done according to the ERS and American Thoracic Society technical standards and percentage of predicted forced expiratory volume in 1 s (FEV_1) calculated using reference values for south Asian patients.[15] Airflow obstruction was defined by an FEV_1/forced vital capacity (FVC) ratio of less than 0·7. True airflow restriction cannot be identified without total lung capacity, which was not measured in the study. Patients with an FEV_1/FVC ratio of 0·7 or more and an FEV_1 and FVC of less than 80% of predicted values were therefore classified as spirometric restriction as previously described in an African population.[16] Breathlessness was evaluated using the modified Medical Research Council Dyspnoea (mMRCD) scale. Quality of life was assessed using the Quality of Life Bronchiectasis Questionnaire (version 3.1) in a subset of patients in English because of the absence of a validated translation in India.[17] CT scans were scored using the modified Reiff score (appendix p 1).[18]

The aetiology of bronchiectasis was recorded as determined by the treating physician. All objective tests and comorbidities were recorded in order to validate the quality of the aetiological diagnosis. Allergic bronchopulmonary aspergillosis was diagnosed according to consensus guidelines.[19] Treatable diagnoses were those referred to in the European bronchiectasis guidelines such as immunodeficiency, allergic bronchopulmonary aspergillosis, and non-tuberculous mycobacterial infection.[19]

No Indian guidelines for management of bronchiectasis exist, and the only international guidelines published are from the ERS in 2017.[20] These international guidelines provided a series of recommendations for management based on nine domains covering diagnosis of the underlying cause of bronchiectasis and treatment.[20] To assess quality of care, we extracted guideline recommendations and tested within our dataset whether patients were managed according to these recommendations. The selected quality standards were aetiological diagnosis (patients should be tested for allergic bronchopulmonary aspergillosis and have immunoglobulins measured), eradication (patients with new *Pseudomonas aeruginosa* infection should have an attempt at eradication), long-term antibiotics (patients with ≥3 exacerbations per year should be treated with oral or inhaled antibiotics), bronchodilators (patients with significant breathlessness should be prescribed long-acting bronchodilators), and respiratory physiotherapy (patients should be taught how to do airway clearance techniques and patients with significant breathlessness should be referred to pulmonary rehabilitation). Patients with spontaneous sputum production should have sputum sent at least once per year for bacterial culture. To reflect the reality that there are often good clinical reasons not to follow guidelines in some cases, we used a threshold of 80% to indicate compliance with guideline-based care.[21]

Comparison with European and US data

To allow demographics and disease burden characteristics to be compared with international data, we did comparisons of the Indian registry data with equivalent data from the published FRIENDS substudy of the European registry (which included data from Israel) and from the US bronchiectasis registry.[2,3] The Indian registry was designed to utilise identical definitions and data fields as the European registry, which in turn was designed to mirror data from the US registry.

Statistical analysis

We presented categorical variables as frequencies and percentages, and analysed statistical differences using a χ^2 test or Fisher's exact test when required. We presented continuous variables as mean and SD, or median and interquartile range (IQR) when data were not distributed normally. Frequency of exacerbations and hospital admissions during the study were analysed with a negative binomial model with time in study as an offset. We presented results as incidence rate ratios (IRRs) with corresponding 95% CIs.

We used logistic regression to calculate adjusted odds ratios (aORs) for categorical outcome variables. In multivariable models, we selected clinically relevant confounder variables using published models for exacerbation frequency in bronchiectasis as a guide.[22] Further details of the models are shown in the appendix (p 1). We defined statistical significance as a two-tailed $p \leq 0 \cdot 05$.

We did the statistical analyses using SPSS (version 22.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or

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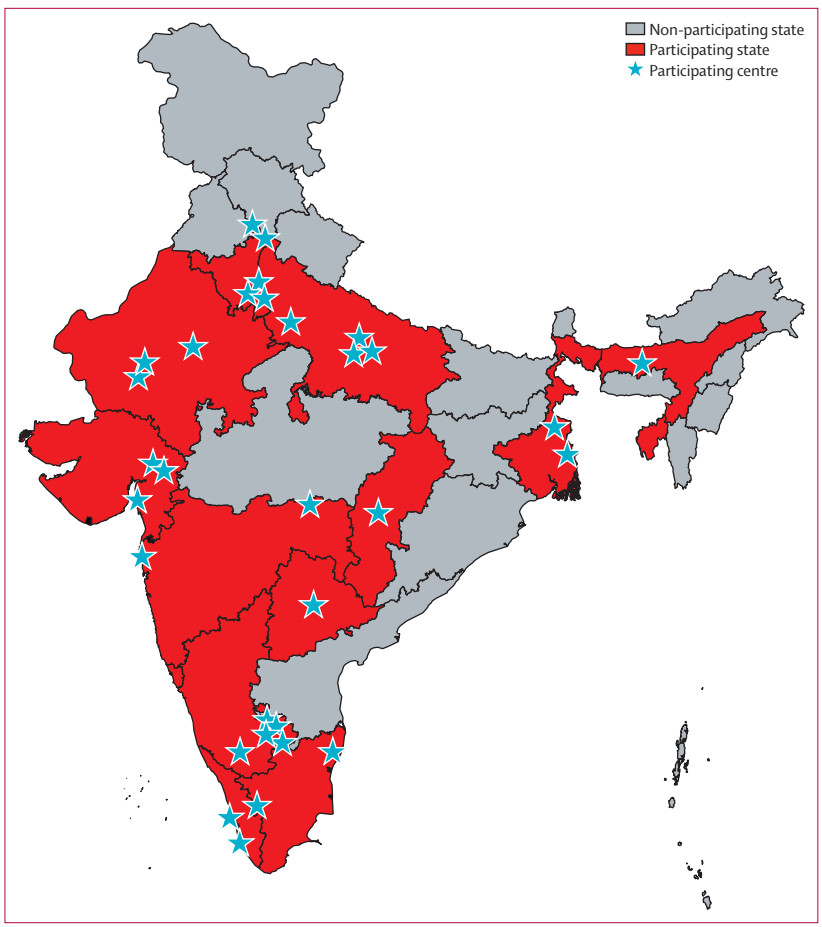

Figure 1: **Location of participating sites in the Indian bronchiectasis registry**

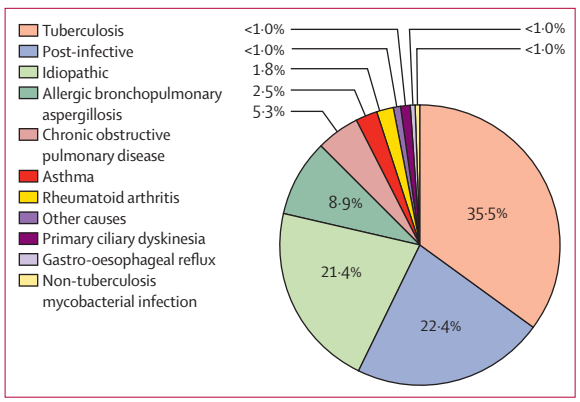

Figure 2: **Underlying causes of bronchiectasis in the Indian bronchiectasis registry**

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writing of the report. The corresponding author had full access to all of the data and final responsibility for the decision to submit for publication.

Results

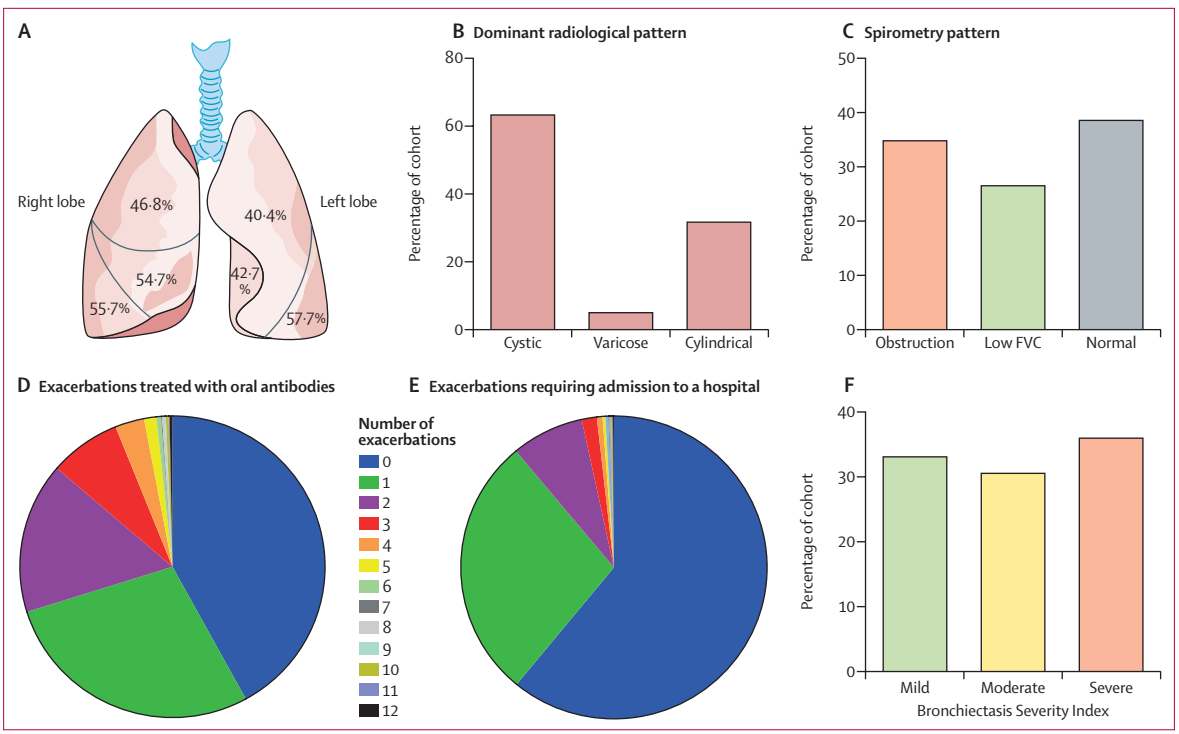
From June 1, 2015, to Sept 1, 2017, 2195 patients were enrolled consecutively from 31 centres across India. The median number of patients enrolled per centre was 58 (IQR 24–113), with the largest centre recruiting 304 patients. Ten (32%) of 31 centres would be regarded as tertiary referral centres and 21 (68%) as secondary care respiratory clinics. Most hospitals served predominantly urban populations (appendix pp 1–3). Patients had a median age of 56 years (IQR 41–66); and of the 2195 patients, 1249 (56·9%) were men and 1576 (71·8%) never smoked.

Figure 2 shows the frequency of reported aetiologies. The most frequent cause was tuberculosis (780 [35·5%] of 2195 patients), followed by a post-infection (491 [22·4%]), and idiopathic bronchiectasis (470 [21·4%]). Allergic bronchopulmonary aspergillosis was also highly prevalent as a cause of bronchiectasis, with 196 (8·9%) of 2195 patients. Less common causes were chronic obstructive pulmonary disease (COPD; 116 [5·3%]), asthma (54 [2·5%]), rheumatoid arthritis (40 [1·8%]), and primary ciliary dyskinesia (18 [<1%]). Non-tuberculous mycobacteria, gastro-oesophageal reflux disease, immunodeficiency, α-1 anti-trypsin deficiency, and tracheobronchomegaly were also represented (figure 2).

Treatable causes, as defined by the ERS, were identified in 232 (10·6%) of 2195 patients and this number increased to 571 (26%) in centres where specific IgE to *Aspergillus fumigatus* and immunoglobulins were tested routinely. Among those where the bronchiectasis was attributed to a previous infection other than tuberculosis, the most frequently reported infections were pneumonia in 351 (71·5%) of 491 patients, other childhood respiratory infections in 143 (29·1%) patients, and pertussis in nine (1·8%) patients. The total adds up to more than 491, as some patients had more than one type of previous infection. Among patients with allergic bronchopulmonary aspergillosis, 42 (21·4%) of 196 were currently treated with oral corticosteroids and 18 (9·2%) were receiving anti-fungal medications at baseline. Of 388 patients tested for allergic bronchopulmonary aspergillosis, the diagnosis was made in 191 (49·2%).

Overall, 916 (41·7%) of 2195 patients had a history of pulmonary tuberculosis. 34 (3·7%) of 916 patients were receiving treatment for active pulmonary tuberculosis at the time of enrolment. 25 (2·7%) were culture positive for *Mycobacterium tuberculosis* at the time of enrolment.

Figure 3 shows the distribution of bronchiectasis according to the lobes affected, showing a relatively equal distribution between bronchiectasis affecting the upper, middle, and lower lobes. Cystic dilatation was the dominant radiological pattern. Despite this radiological severity, the majority of the patients (1284 [58·5%] of 2195) did not report production of daily sputum. The appendix (pp 3–4) shows clinical factors associated with sputum production. Patients with more severe disease, *P aeruginosa* infection, and cystic dilatation on CT were more likely to be sputum producers. Currently macrolide use was associated with lack of sputum production (appendix pp 3–4).



See Online for appendix

Figure 3: **Extent and severity of bronchiectasis in the Indian bronchiectasis registry**
(A) Radiological distribution of bronchiectasis. Percentages refer to the lobes affected with the lingula treated as a separate lobe. Percentages add up to more than 100% as patients can have multiple lobes affected. (B) Dominant radiological pattern on CT. (C) Spirometry pattern at baseline. Low FVC was defined as spirometric restriction; obstruction was defined by FEV_1/FVC <0·7 and normal spirometry required an FEV_1 and FVC above 80% of predicted value. (D) Number of exacerbations treated with oral antibiotics. (E) Number of exacerbations requiring admission to a hospital. (F) Distribution of the multidimensional Bronchiectasis Severity Index. FEV_1/FVC=ratio of forced expiratory volume in 1 s/forced vital capacity.

The mean frequency of all exacerbations inluding severe was 1·15 per year (SD 1·5) and the mean frequency of severe exacerbations requiring hospital admission was 0·55 per year (SD 0·9). Using the bronchiectasis severity index score, we observed 728 (33·2%) of 2195 with mild bronchiectasis, 674 (30·7%) with moderate bronchiectasis, and 793 (36·1%) with severe bronchiectasis (figure 3F). The frequent exacerbator phenotype (≥3 per year) was seen in 529 (24·1%) of 2195 patients. A comparison of characteristics of frequent and infrequent exacerbators is shown in the appendix (pp 4–6).

Breathlessness was a common symptom among the participants. 169 (7·7%) of 2195 patients had an mMRCD grade 4, 394 (17·9%) had an mMRCD grade 3, 638 (29·1%) reported a grade 2, 646 (29·4%) a grade 1, and 348 (15·9%) a grade 0. Breathlessness, daily sputum production, exacerbations, and chronic airway infection were independently associated with worse quality of life scores in linear regression models suggesting these factors are the major drivers of poor quality of life in Indian patients with bronchiectasis (appendix pp 3–4).

In terms of the severity of FEV_1 impairment, the overall median FEV_1 was 1·31 L (IQR 0·88–1·84), which translated to a median predicted percentage of 61·4% (IQR 41·9–80·5). Airflow obstruction was the predominant spirometric abnormality affecting 764 (34·8%) of 2195 patients. Low FVC (defined as spirometric restriction) was, however, surprisingly common, affecting 585 (26·7%) of 2195 patients. Of the 764 patients with airflow obstruction, 706 (92·4%) had fixed airflow obstruction on post-bronchodilator spirometry. Pre-bronchodilator spirometry only was available for the other 58 (7·6%) participants.

We did a logistic regression model to identify variables associated with this low FVC phenotype and identified a strong association with post-tuberculosis bronchiectasis (aOR 2·02, 95% CI 1·45–2·82; p<0·0001; appendix pp 6–7).

1299 (59·2%) of 2195 patients had at least one sputum sample taken in the year before the baseline visit. The most frequent isolated organism was *P aeruginosa* in 301 (13·7%) patients, followed by Enterobacteriaceae species (215 [9·8%]) such as *Escherichia* and *Klebsiella pneumoniae*. *Acinetobacter* sp was isolated in 22 (1·0%) patients. Organisms commonly reported in western Europe and US cohorts such as *Haemophilus influenzae* (11 [0·5%] of 2195 patients), *Moraxella catarrhalis* (22 [1·0%]), *Streptococcus pneumoniae* (18 [0·8%]), *Staphylococcus aureus* (50 [2·3%]), and non-tuberculous mycobacteria (eight [0·4%]) were uncommon in the participants.

Figure 4 shows the most commonly prescribed treatments. These treatments included inhaled

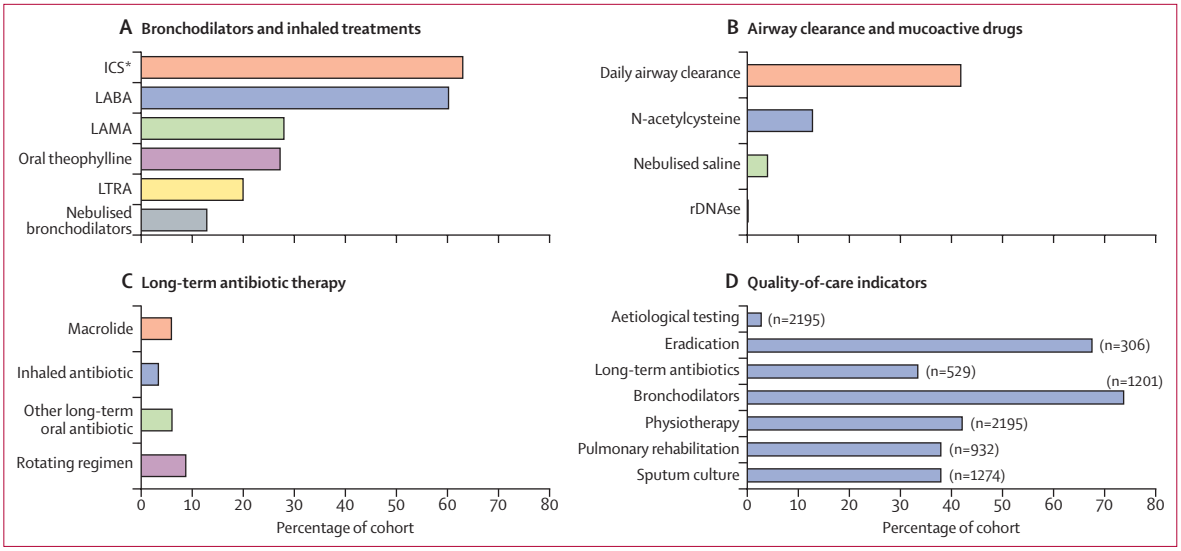


Figure 4: **Most commonly prescribed treatments for bronchiectasis and the quality-of-care indicators in the Indian bronchiectasis registry**
(A) Bronchodilators and inhaled treatments. (B) Airway clearance and mucoactive drugs. (C) Long-term antibiotic therapy. (D) Quality standards for bronchiectasis management in India. The numbers indicate the number of patients eligible. ICS=inhaled corticosteroids. LABA=long-acting β agonist. LAMA=long-acting muscarinic antagonist. LTRA=leukotriene receptor antagonist. *Includes ICS in combination with LABA, ICS monotherapy, and ICS, LABA, and LAMA in a single inhaler.

bronchodilators, long-term antibiotics, mucoactive drugs, and chest physiotherapy. 1387 (63·2%) of 2195 patients were receiving inhaled corticosteroids, and in 1242 (56·6%) of patients this treatment was a fixed combination of an inhaled corticosteroid with a long-acting β agonist. N-acetylcysteine was the most commonly used mucoactive drug. Drugs such as theophylline, leukotriene receptor antagonists, and bronchodilators were frequently used in patients without a history of asthma or COPD.

Long-term antibiotics were infrequently used, with the most common regimens being a rotating long-term antibiotic regimen—eg, targeted oral antibiotics for several months of the year (195 [8·9%] of 2195 patients) and long-term oral antibiotics other than macrolide (136 [6·2%]), which include long-term amoxicillin-clavulanic acid (70 [3·2%]), fluoroquinolones (25 [1·1%]), and tetracyclines (17 [1·0%]).

Using the ERS guideline recommendations as a benchmark, we observed low adherence to guideline-recommended care.[21] Only 388 patients were tested for allergic bronchopulmonary aspergillosis and 82 patients had been tested for immunoglobulins. Consequently, only 67 (3·1%) of 2195 patients were tested according to the ERS guideline recommendations. Among 306 patients with a history of *P aeruginosa* infection, eradication had been attempted in 207 (67·6%) patients. Out of 529 patients with three or more exacerbations per year, 351 (66·4%) patients were receiving no prophylactic therapy.

1201 patients had an mMRCD score of 2 or more. Of these patients, 315 (26·2%) patients were not receiving any long-acting bronchodilators. 927 (42·2%) of 2195 patients with bronchiectasis in India had received training in airway clearance. 515 (40·4%) of 1274 patients who complained of daily sputum production had been trained in airway clearance techniques. After excluding patients that were not suitable for pulmonary rehabilitation because of comorbidities and those who declined to attend, 932 patients had an mMRCD score of 2 or more and would be eligible for referral to pulmonary rehabilitation, of which 355 (38·1%) patients had attended pulmonary rehabilitation. Figure 4D summarises the data and indicates that currently none of these domains achieve the 80% target for quality standard adherence.

Differences in patient characteristics were observed according to underlying aetiology and other disease characteristics. Table 1 shows a comparison of patient characteristics according to the underlying aetiology assigned by the treating clinician. Comparing these groups, patients with asthma and allergic broncho-pulmonary aspergillosis were younger than other subgroups, and patients with COPD were more likely to be men. Post-tuberculosis bronchiectasis showed characteristics in terms of severity, microbiology, and demographics that were similar to idiopathic and post-infective disease. Patients with overlapping bronchiectasis and COPD tended to have more severe disease.

Other key phenotypes other than those associated with aetiology, include the so-called frequent exacerbator and *P aeruginosa* infection as a distinct phenotype.[22] Examining the frequent exacerbator phenotype in the Indian registry, exacerbations during follow-up were most strongly associated with men (adjusted IRR 1·17, 95% CI 1·03–1·32; p=0·015), *P aeruginosa* infection (1·29, 1·10–1·50; p=0·001), a history of pulmonary tuberculosis (1·20, 1·07–1·34; p=0·002), mMRCD score (1·32, 1·25–1·39; p<0·0001), daily sputum production (1·16, 1·03–1·30; p=0·013), and radiological severity

	Post-tuberculosis (n=780)	Idiopathic (n=469)	Post-infective (non-tuberculosis; n=491)	Allergic bronchopulmonary aspergillosis (n=196)	Chronic obstructive pulmonary disease (n=116)	Asthma (n=54)	Other (n=89)
Demographics							
Age (years)	57 (44–67)	56 (43–66)	53 (39–64)	46 (33–57)	64 (56–70)	52 (45–62)	56 (39–63)
Men	465 (59·6%)	265 (56·5%)	270 (55·0%)	102 (52·0%)	84 (72·4%)	23 (42·6%)	40 (44·9%)
Body-mass index	21·0 (18·1–23·8)	22·2 (19·0–25·3)	21·6 (18·7–24·4)	21·6 (18·8–24·9)	22·6 (19·4–26·4)	24·0 (22·3–26·0)	20·9 (17·3–24·0)
Ex-smokers	223 (28·6%)	78 (16·6%)	110 (22·4%)	16 (8·2%)	56 (48·3%)	8 (14·8%)	15 (16·9%)
Current smokers	61 (7·8%)	18 (3·8%)	12 (2·4%)	3 (1·5%)	16 (13·8%)	2 (3·7%)	1 (1·1%)
Comorbidity							
Ischaemic heart disease	97 (12·4%)	92 (19·6%)	64 (13·0%)	25 (12·8%)	36 (31·0%)	20 (37·0%)	21 (23·6%)
Stroke	6 (0·8%)	0	3 (0·6%)	0	0	0	0
Diabetes	122 (15·6%)	67 (14·3%)	61 (12·4%)	11 (5·6%)	37 (31·9%)	9 (16·7%)	8 (9·0%)
Liver disease	13 (1·7%)	3 (0·6%)	2 (0·4%)	0	0	0	0
Chronic renal failure	9 (1·2%)	4 (0·9%)	5 (1·0%)	2 (1·0%)	3 (2·6%)	0	1 (1·1%)
Chronic obstructive pulmonary disease	213 (27·3%)	75 (16·0%)	85 (17·3%)	11 (5·6%)	NA	0	15 (16·9%)
Asthma	79 (10·1%)	91 (19·4%)	81 (16·5%)	158 (80·6%)	8 (6·9%)	NA	12 (13·5%)
Osteoporosis	56 (7·2%)	8 (1·7%)	29 (5·9%)	11 (5·6%)	13 (11·2%)	7 (13·0%)	6 (6·7%)
Gastro-oesophageal reflux disease	140 (17·9%)	45 (9·6%)	100 (20·4%)	18 (9·2%)	20 (17·2%)	4 (7·4%)	19 (21·3%)
Solid tumour	7 (0·9%)	3 (0·6%)	4 (0·8%)	0	2 (1·7%)	0	1 (1·1%)
Disease severity							
BSI score	7 (4–10)	6 (3–9)	7 (4–10)	5 (2–9)	9 (5–12)	6 (3–9)	8 (5–12)
BSI score risk class							
Mild	241 (30·9%)	173 (36·9%)	157 (32·0%)	97 (49·5%)	19 (16·4%)	22 (40·7%)	19 (21·3%)
Moderate	230 (29·5%)	158 (33·7%)	162 (33·0%)	46 (23·5%)	36 (31·0%)	14 (25·9%)	28 (31·5%)
Severe	309 (39·6%)	138 (29·4%)	172 (35·0%)	53 (27·0%)	61 (52·6%)	18 (33·3%)	42 (47·2%)
Radiological status							
Reiff score	6 (3–9)	6 (3–9)	6 (3–9)	6 (5–12)	6 (3–9)	6 (2–9)	6 (4–9)
Cystic dilatation	436 (55·9%)	289 (61·6%)	362 (73·7%)	141 (71·9%)	80 (69·0%)	28 (51·9%)	54 (60·7%)
Clinical status							
Sputum volume (mL/day)	10 (0–30)	5 (0–30)	10 (0–30)	5 (0–20)	20 (5–40)	10 (0–30)	10 (0–28)
Modified Medical Research Council Dyspnoea score	2 (1–3)	1 (1–2)	2 (1–3)	1 (0–2)	2 (2–3)	2 (1–3)	2 (1–3)
Exacerbations in the previous year	1 (0–3)	1 (0–2)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	2 (1–3)
≥1 hospital admission in the previous year	335 (42·9%)	213 (45·4%)	171 (34·8%)	57 (29·1%)	63 (54·3%)	21 (38·9%)	42 (47·2%)
Functional status							
FEV_1 (% predicted)	63·9 (46·9–79·9)	58·7 (38·6–79·3)	52·8 (36·5–70·0)	55·4 (39·7–77·4)	47·8 (35·9–79·2)	63·2 (46·4–80·1)	60·6 (36·5–85·4)
Microbiology							
Pseudomonas aeruginosa	105 (13·5%)	66 (14·1%)	67 (13·6%)	19 (9·7%)	19 (16·4%)	5 (9·3%)	20 (22·5%)
Haemophilus influenzae	1 (0·1%)	6 (1·3%)	3 (0·6%)	0	0	1 (1·9%)	0
Staphylococcus aureus	34 (4·4%)	5 (1·1%)	10 (2·0%)	0	1 (0·9%)	0	0
Moraxella catarrhalis	7 (0·9%)	6 (1·3%)	8 (1·6%)	1 (0·5%)	0	0	0
Enterobacteriaceae	81 (10·4%)	43 (9·2%)	43 (8·8%)	13 (6·6%)	16 (13·8%)	8 (14·8%)	11 (12·4%)
Treatment							
Long-term macrolide treatment	51 (6·5%)	15 (3·2%)	47 (9·6%)	4 (2·0%)	9 (6·9%)	2 (3·7%)	7 (7·9%)
Other long-term oral antibiotic treatments	54 (6·5%)	20 (4·3%)	46 (9·4%)	7 (3·6%)	3 (2·6%)	0	7 (7·9%)
Inhaled antibiotic treatment	14 (1·8%)	10 (2·1%)	20 (4·1%)	19 (9·7%)	9 (7·8%)	3 (5·6%)	4 (4·5%)
Quality of life							
Quality-of-life bronchiectasis questionnaire (Respiratory Symptom Score)	66·7 (44·4–77·8)	59·3 (38·1–81·5)	63·0 (51·9–70·4)	66·7 (55·6–85·2)	57·5 (41·6–66·7)	63·0 (37·0–69·0)	51·9 (19·0–66·7)

Data are median (IQR) or n (%). BSI=Bronchiectasis Severity Index. FEV_1=forced expiratory volume in 1 s. NA=not applicable.

Table 1: **Characteristics and severity of disease in patients according to the underlying aetiology assigned by the clinician**

	India (n=2195)	Europe* (n=2596)	p value
Demographics			
Age (years)	56 (41–66)	67 (57–74)	<0·0001
Men	1249 (56·9%)	1010 (38·9%)	<0·0001
Body-mass index	21·5 (18·5–24·5)	24·8 (21·8–28·1)	<0·0001
Current or former smokers	619 (28·2%)	990 (38·1%)	<0·0001
Comorbidity			
Ischaemic heart disease	355 (16·2%)	453 (17·5%)	0·2
Stroke	9 (0·4%)	152 (5·9%)	<0·0001
Diabetes	315 (14·4%)	260 (10·0%)	<0·0001
Liver disease	18 (0·8%)	41 (1·6%)	0·0002
Chronic renal failure	26 (1·2%)	154 (5·9%)	<0·0001
Chronic obstructive pulmonary disease	512 (23·3%)	431 (16·6%)	<0·0001
Asthma	485 (22·1%)	226 (8·7%)	<0·0001
Osteoporosis	130 (5·9%)	192 (7·4%)	0·04
Gastro-oesophageal reflux disease	346 (15·8%)	394 (15·2%)	0·6
Solid tumour	17 (0·8%)	164 (6·3%)	<0·0001
Disease severity			
BSI score	7 (3–10)	6 (4–10)	<0·0001
BSI score risk class			
Mild	728 (33·2%)	753 (29·0%)	0·0004
Moderate	674 (30·7%)	926 (35·7%)	
Severe	793 (36·1%)	917 (35·3%)	
Radiological status			
Reiff score	6 (3–9)	4 (2–6)	<0·0001
Clinical status			
Modified Medical Research Council Dyspnoea score	2 (1–3)	2 (1–3)	0·3
Exacerbations in the previous year	1 (0–2)	2 (0–3)	<0·0001
≥1 hospital admission in the previous year	851 (38·8%)	672 (25·9%)	<0·0001
Functional status			
FEV_1 (% predicted)	61·4 (41·9–80·5)	73·8 (54·0–92·1%)	<0·0001
Microbiology			
Pseudomonas aeruginosa	301 (13·7%)	389 (15·0%)	0·2
Haemophilus influenzae	11 (0·5%)	569 (21·9%)	<0·0001
Staphylococcus aureus	50 (2·3%)	156 (6·0%)	<0·0001
Moraxella catarrhalis	22 (1·0%)	154 (5·9%)	<0·0001
Enterobacteriaceae	215 (9·8%)	158 (6·1%)	<0·0001
Treatment			
Long-term oral antibiotic treatment	271 (12·3%)	503 (19·4%)	<0·0001
Inhaled antibiotic treatment	79 (3·6%)	166 (6·4%)	<0·0001

Data are median (IQR) or n (%). BSI=Bronchiectasis Severity Index. FEV_1=forced expiratory volume in 1 s. *Includes patients from Israel.

Table 2: **Comparison of patient characteristics between India and Europe**

of disease (1·03, 1·01–1·04; p<0·0001). Macrolide treatment was also associated with a higher frequency of exacerbations (adjusted IRR 1·48, 95% CI 1·19–1·83; p<0·0001). The appendix (pp 8–9) shows the full results of the model and the determinants of poor quality of life.

2596 patients from Europe and Israel were included. We refer to this comparative group as Europe for brevity, and the 2596 patients were compared with the cohort of patients from India (table 2). Significant differences were observed in the majority of demographic, comorbidity, disease severity, radiological, clinical, functional status, and microbiological domains. Indian patients were younger, more likely to be men, and had a lower body-mass index (BMI) than their European counterparts. Consistent with a younger age, there were less comorbidities, except for a higher incidence of diabetes. Indian patients were more likely to be classified as severe using the Bronchiectasis Severity Index and had more extensive, cystic, radiological disease. Outpatient exacerbations were less common but hospitalised exacerbations were more common in India than in Europe. FEV_1 percentage predicted was lower in Indian patients than in European patients. Both long-term oral and inhaled antibiotic treatments were more commonly used in Europe than in India (table 2).

In a negative binomial model, Indian patients were more likely to be admitted to hospital during the study than European patients (adjusted IRR 1·21, 95% CI 1·04–1·40; p=0·011) but had a lower frequency of reported outpatient exacerbations (0·60, 0·55–0·66; p<0·0001).

Long-term oral antibiotic prophylaxis was less frequently used in India than in Europe (OR 0·58, 95% CI 0·44–0·68; p<0·0001), a difference that persisted after adjustment for patient characteristics (aOR 0·80, 95% CI 0·65–0·98; p=0·03). Patients in India were less likely to receive inhaled antibiotics than in Europe (OR 0·58, 95% CI 0·44–0·77; p<0·0001) but this result was not significant in the multivariate analysis (aOR 0·78, 95% CI 0·52–1·16; p=0·26).

Data from patients in the Indian registry were compared with published data from the US registry (n=1826). The patients from the US registry had a mean age of 64 years (SD 14). 721 (39·7%) of 1815 were current or former smokers, with a mean BMI of 23·2 (SD 5·7). Compared with these values, Indian patients were significantly younger, less likely to have a smoking history, and had a lower BMI. In terms of microbiology, 470 (33·4%) of 1406 of the US registry participants had at least one isolation of *P aeruginosa* while other pathogens included *S aureus* (170 [12·1%]), *H influenzae* (116 [8·3%]) and non-tuberculous mycobacterial infection (657 [50·0%] of 1314). Indian patients therefore had a significantly lower isolation of *P aeruginosa* and non-tuberculous mycobacterial infection (both p<0·0001). Oral antibiotic prophylaxis was used in 125 (7·1%) of the US registry participants, and inhaled antibiotics were used in 178 (10·1%). Indian patients were therefore more likely to receive oral antibiotic prophylaxis than those in the US registry but were less likely to receive inhaled antibiotics. A comparison of microbiology in the Indian, European, and US registries is shown in the appendix (pp 9–10).

Discussion

This study is, to our knowledge, the first large-scale registry study of patients with adult bronchiectasis done

in a lower-middle-income country. The results show the high severity of disease in India as well as the striking differences in patient characteristics, aetiology, microbiology, and standards of care in India compared with Europe and the USA. Key findings include that patients in India have more severe bronchiectasis as evaluated by prognostic scores. This effect is regardless of a younger age, and this increased severity is driven by more extensive radiological disease with a remarkably high rate of cystic dilatation, and a higher risk of admission to hospital for severe exacerbations.

The aetiology of bronchiectasis in India was different to that observed in Europe and the USA. Consistent with the high prevalence of tuberculosis in the Indian subcontinent, tuberculosis was the most frequent underlying cause of bronchiectasis and when combined with other severe infections, in which infection accounted for 58% of all cases of bronchiectasis.[23] Lung destruction secondary to tuberculosis including bronchiectasis is well described and the high background incidence of tuberculosis could be one of the explanations for the high frequency of cystic bronchiectasis observed in India.[23] A systematic review of studies that did CT systematically in patients after recovery from tuberculosis reported bronchiectasis in 40–80% of patients.[12] The largest such study, which included 385 patients with tuberculosis in Blantyre, Malawi, found moderate-to-severe bronchiectasis in 44·2% of scans.[13] If such findings were translated to India with an estimate of 2·8 million cases of tuberculosis per year, the burden of bronchiectasis—a lifelong chronic condition—would be vast. Bronchiectasis is also thought to be associated with severe infections particularly during childhood and a high frequency of severe disease including cystic bronchiectasis has been reported in indigenous communities with poor access to health care.[24]

Our study identified a relatively high frequency of allergic bronchopulmonary aspergillosis in India. Strikingly, nearly 50% of patients tested for allergic bronchopulmonary aspergillosis had the disease, suggesting either a high prevalence or that testing was restricted only to those individuals with a very strong clinical suspicion of the disorder. Mac Aogáin and colleagues[19] have recently reported a serological frequency of 18% for allergic bronchopulmonary aspergillosis in a combined European and Asian cohort with an association between sensitisation and frequency of exacerbations.[19] Because allergic bronchopulmonary aspergillosis is a treatable cause of frequent exacerbations and lung function decline, we recommend increased screening for allergic bronchopulmonary aspergillosis in India.

The microbiology data in our study were limited by the relatively low rate of sputum sampling observed in routine clinical practice in India. Nevertheless, striking differences in microbiology were observed with low rates of typical pathogens found in Europeans such as *H influenzae* but similar rates of *P aeruginosa* to Europe and the USA.[22] Higher rates of Enterobacteriaceae were also observed. This observation could reflect differences in patient characteristics or environmental conditions favouring the growth of certain organisms, including community antibiotic use, but the possibility that technical factors in microbiological sampling and laboratory procedures in India might affect the results should also be considered. *H influenzae* in particular can be challenging to isolate and might lose viability after delays in processing. Previous studies suggest difficulties in isolating *H influenzae* in low-income and middle-income countries.[25] Further studies are needed to clarify this and future studies should ideally include molecular analysis and metagenomics, which can overcome some of these limitations.

Treatment of bronchiectasis in India was diverse but included a high frequency of bronchodilators and inhaled corticosteroids.[26] In that sense, it could be suggested that many patients with bronchiectasis are treated similarly to those with COPD, as the majority of patients receiving inhaled corticosteroids did not have a history of COPD or asthma. This effect might be in part driven by the availability of inhaled corticosteroids in India and their relatively low cost in a health-care system where patients are required to pay for their medications themselves. Inhaled corticosteroid use in bronchiectasis is contrary to current ERS guidelines. Currently, high-quality randomised trials are required to determine whether inhaled corticosteroid use has any beneficial effects in this patient population.[26] One of the most effective and least costly interventions for bronchiectasis is airway clearance exercises.[27] Unfortunately, our data suggests these interventions are underutilised in India, in common with many health-care systems, with substantial variations in care observed between different centres. Recent data suggest that airway clearance can cut the number of exacerbations and improve quality of life. Future studies should examine how the use of airway clearance could be increased and optimised.[27] Oral and inhaled prophylactic antibiotics were also used less frequently in India than in other countries. This finding is notable as, to date, macrolides are among only a few therapies proven to reduce exacerbations.[28]

We defined risk factors for exacerbations in Indian patients and identified some important messages. *P aeruginosa* was strongly associated with a risk of exacerbations, confirming airway infection as a key treatable trait in India as in Europe and the USA.[2,3,6] More severe disease reflected by radiology or symptoms were also associated with higher exacerbations. The reason that being a male patient was associated with more exacerbations than being a female patient even after adjustment for other factors is intriguing and requires further study. Even after adjustment for confounders, a history of pulmonary tuberculosis was associated with more frequent exacerbations in this population, which suggests that tuberculosis might be an important contributor to the high severity of disease that we

observed in the Indian context. We observed that the number of exacerbations treated with oral antibiotics was relatively low in India, whereas admission to hospital due to exacerbations was more common in India than in Europe and the USA. This finding might reflect health-care system organisation that is more skewed towards hospital-based care, but might also reflect differences in severity of disease and therefore risk of more severe exacerbations. It is intriguing that a recent phase 3 trial of inhaled dry powder ciprofloxacin, which was done in eastern European countries with a high frequency of tuberculosis, also reported very low frequencies of moderate exacerbations, even in a population with a history of two more exacerbations in the past, and quality of life scores suggesting a high burden of symptoms.[8,9]

Our work nevertheless confirms that bronchiectasis in Asian patients frequently follows an aggressive course with onset at an earlier age, more extensive lung damage, and severe symptoms compared with populations in Europe and the USA. Similar data from China support that this finding is not unique to India.[4] Severity of disease assessment tools such as the Bronchiectasis Severity Index were derived and validated predominantly in populations in developed countries.[18] We found nearly all of the components of these scores, including age, radiology, microbiology, functional status, and exacerbations were markedly different in India compared with the countries where the Bronchiectasis Severity Index and equivalent scores were developed. Such tools should be used with caution in Asian populations and specific disease severity tools for these patients might be required.

Our work suggests the need for caution in interpreting the results of bronchiectasis studies arising from different geographical regions.[29] Patients in India were markedly different from those reported in other countries. Consequently, the results of trials or cohort studies in Europe, USA, or Australasia might not be applicable to very different patients in India or elsewhere. This discrepancy suggests the need to do studies in different patient populations and to carefully phenotype patients. It also suggests the need for care in selecting patients for randomised trials.

Our work should serve as a baseline for efforts to improve the quality of care for bronchiectasis in India. The study nevertheless has limitations. These initial results are cross-sectional and ongoing data collection in the registry will allow studies into lung function decline and long-term mortality.[30] The study did not collect data for household biomass exposure, which might be important in respiratory morbidity in the region. Some aspects of our epidemiological data are limited by the quality of care; underuse of aetiological testing, which leads to more patients being classified as idiopathic or post-infective; and the microbiological data, which are likely to underestimate the frequency of chronic infection because of inadequate sputum sampling. Nevertheless, the strength of the data reflect what clinicians will encounter in daily practice.

In conclusion, we present unique epidemiological data for bronchiectasis in India that will be important to inform quality improvement efforts in India as well as future clinical trial design and disease understanding.

Contributors

RD, MLC, SL, SuS, StA, and JDC did the study design. All authors contributed to patient enrolment and data collection. RD, SL, and JDC analysed the data. RD, SL, and JDC drafted the manuscript. All authors reviewed the manuscript and approved it for submission.

Declaration of interests

SL reports a grant from Glenmark Pharmaceuticals. ADS reports consultancy or speaker fees from AstraZeneca, Bayer, Chiesi, Pfizer, and Insmed. AT reports personal fees or grants from Pfizer, Merck Sharp & Dohme, Polyphor, and Medimmune. PGC reports personal fees from AstraZeneca, Boehringer Ingelheim, and Chiesi. JDC reports grants and personal fees from GlaxoSmithKline, AstraZeneca, Pfizer, Bayer, Grifols, Napp, Aradigm Corporation, and Insmed. All other authors declare no competing interests.

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